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An Introduction to Hydrogels and Some Recent Applications

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Abstract

Hydrogels have existed for more than half a century, and today they have many applications in various processes ranging from industrial to biological. There are numerous original papers, reviews, and monographs focused on the synthesis, properties, and applications of hydrogels. This chapter covers the fundamental aspects and several applications of hydrogels based on the old and the most recent publications in this field.

Keywords: Hydrogels, Classification, Synthesis, Applications, Drug delivery, Spinal cord injury, Supercapacitor

1. Introduction

A hydrogel is a three-dimensional (3D) network of hydrophilic polymers that can swell in water and hold a large amount of water while maintaining the structure due to chemical or physical cross-linking of individual polymer chains. Hydrogels were first reported by Wichterle and Lím (1960) [1]. By definition, water must constitute at least 10% of the total weight (or volume) for a material to be a hydrogel. Hydrogels also possess a degree of flexibility very similar to natural tissue due to their significant water content. The hydrophilicity of the network is due to the presence of hydrophilic groups such as $-\text{NH}_2$, $-\text{COOH}$, $-\text{OH}$, $-\text{CONH}_2$, $-\text{CONH}-$, and $-\text{SO}_3\text{H}$.

Hydrogels undergo a significant volume phase transition or gel-sol phase transition in response to certain physical and chemical stimuli. The physical stimuli include temperature, electric and magnetic fields, solvent composition, light intensity, and pressure, while the

chemical or biochemical stimuli include pH, ions, and specific chemical compositions. However, in most cases such conformational transitions are reversible; therefore, the hydrogels are capable of returning to their initial state after a reaction as soon as the trigger is removed. The response of hydrogels to external stimuli is mainly determined by the nature of the monomer, charge density, pendant chains, and the degree of cross-linkage. The magnitude of response is also directly proportional to the applied external stimulus.

There are numerous original papers, reviews, and monographs focused on the synthesis, properties, and applications of hydrogels. This chapter covers the fundamental aspects and application areas of hydrogels.

2. Classifications of hydrogels

The literature reports a number of classifications of hydrogels and presents several views. Hydrogels are mainly formed from biopolymers and/or polyelectrolytes. Concerning definitions of hydrogel types, according to the source, hydrogels can be divided into those formed from natural polymers and those formed from synthetic polymers [2]. Depending on the ionic charges on the bound groups, hydrogels may be cationic, anionic, or neutral. The types of cross-linking agents also can be the criteria for classification.

Hydrogels can be physical, chemical, or biochemical. Physical gels can undergo a transition from liquid to a gel in response to a change in environmental conditions such as temperature, ionic concentration, pH, or other conditions such as mixing of two components. Chemical gels use covalent bonding that introduces mechanical integrity and degradation resistance compared to other weak materials. In biochemical hydrogels, biological agents like enzymes or amino acids participate in the gelation process.

It is also possible to divide hydrogels into groups based on their structure: amorphous, semicrystalline, crystalline, and hydrocolloid aggregates [3]. **Figure 1** clearly represents the classification of hydrogels based on their source and properties, along with detailed classifi-



Figure 1. Classification of hydrogels based on the different properties.

cations based on their response, that is, physically, chemically, and biochemically responsive hydrogels (**Figures 2 and 3**).

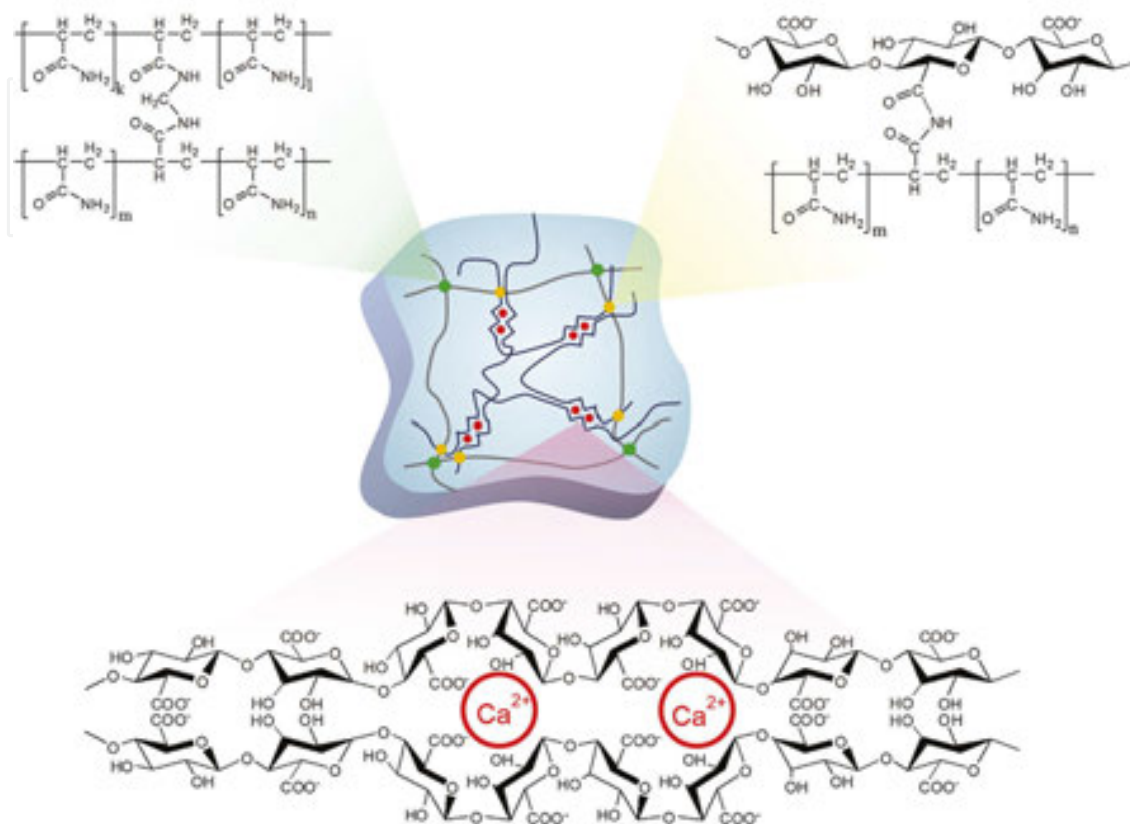


Figure 2. In situ hydrogel formation using chemical cross-linking and ionic interaction between alginate and calcium ions [61, 62].

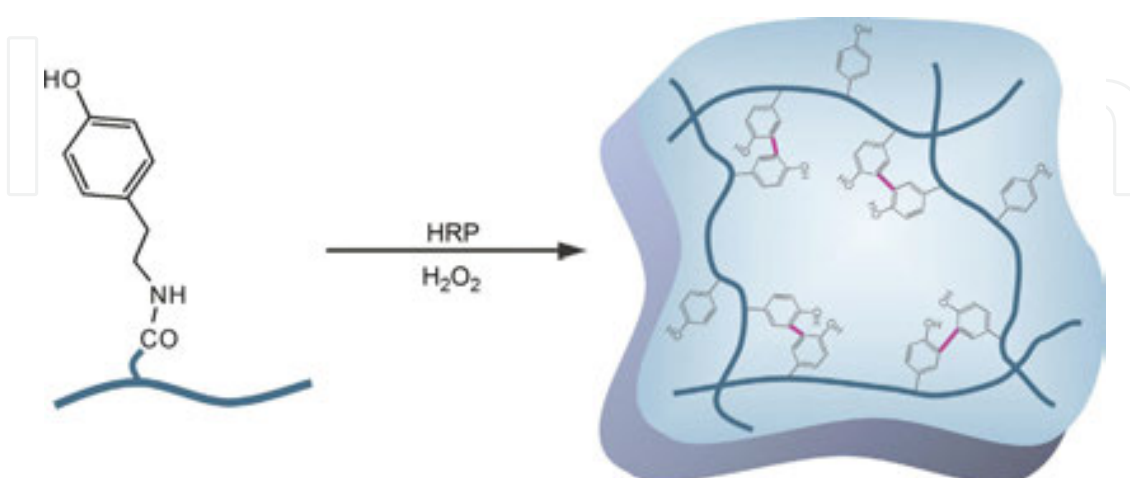


Figure 3. In situ hydrogel formation using an enzymatic cross-linking reaction with horseradish peroxidase (HRP) and H_2O_2 [62].

3. Synthesis of hydrogels

Based on the methods of preparation, hydrogels may be classified as homopolymer, copolymer, semi-interpenetrating network (semi-IPN) and interpenetrating network (IPN). **Table 1** indicates some examples.

Type of hydrogel	Monomer	Cross-linker	Specific reaction conditions	References	Applications
Homopolymer	Poly(2-hydroxyethyl methacrylate) (PHEMA)	Polyethylene glycol dimethacrylate	Presence of benzoin isobutyl ether as the UV-sensitive initiator	[4, 5]	Drug delivery systems, contact lenses, scaffolds for protein recombination
	2-Hydroxyethyl methacrylate (HEMA)	TEGDMA (triethylene glycol dimethacrylate)			
	Polyethylene glycol (PEG)				Wound healing and functional tissues production
Copolymer	Methacrylic acid (MAA)	Tetra(ethylene glycol) dimethacrylate	Free-radical photopolymerization	[4–7]	Drug delivery, hydrogel dressing material
	PEG-PEGMA				
	Carboxymethyl cellulose (CMC)				
Semi-inter penetrating network	Polyvinylpyrrolidone (PVP)				
	Acrylamide/acrylic acid copolymer	<i>N,N'</i> -methylene bisacrylamide	Template copolymerization	[75]	Drug delivery
Inter penetrating network	Linear cationic polyallylammonium chloride				
	Poly(<i>N</i> -isopropyl acrylamide) (PNIPAM)	<i>N,N'</i> -methylene bisacrylamide	<i>N,N,N',N'</i> -tetramethylethylenediamine (TEMED), ammonium persulphate (APS) and Presence of UV light	[76]	Drug delivery
Self-assembling peptide systems	Chitosan				
	Acrylate-modified PEG and acrylate-modified hyaluronic acid	No cross-linking agent	Presence of UV light and a photo-initiator	[63, 49]	Tissue regeneration
	Heparin		EDC/sulfo-NHS solution and low temperature		
	Amine end-functionalized 4-arm star-PEG				

Table 1. Some examples of synthesis methods and applications of hydrogels.

Homopolymers contain only one type of monomer in their structure, and based on the nature of the monomer and the technique used for polymerization, they may have a cross-linked structure (**Figure 4**).

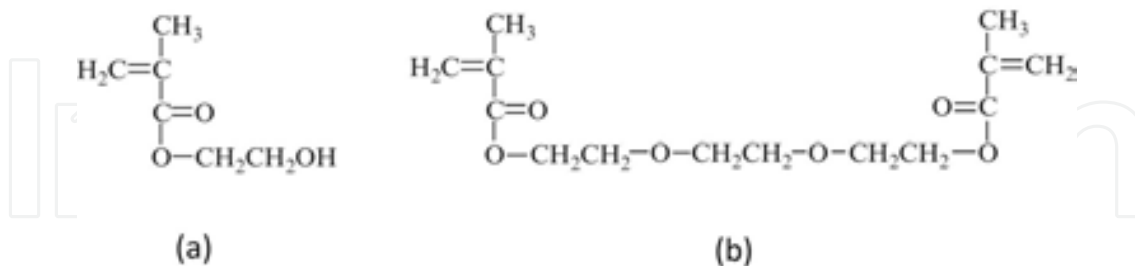


Figure 4. Structures of (a) HEMA and (b) TEGDMA.

Copolymeric hydrogels are composed of two types of monomers, of which at least one is hydrophilic in nature (**Figures 5–7**).

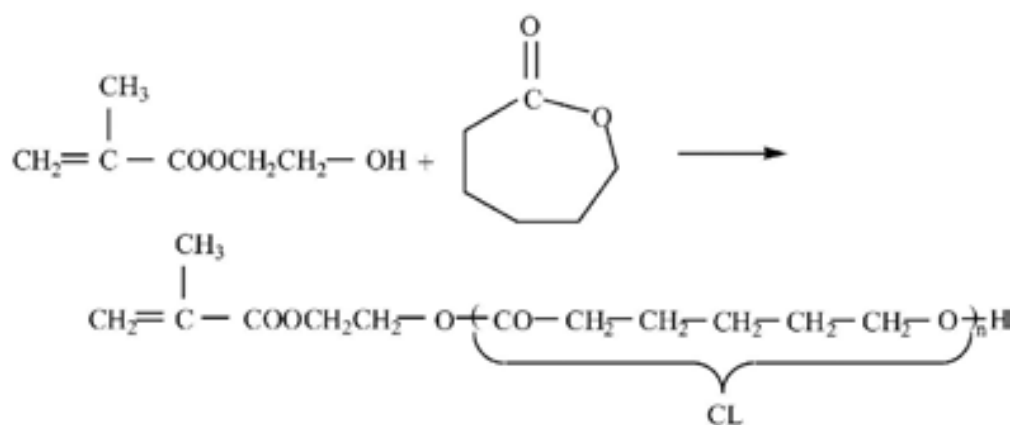


Figure 5. Synthesis of the poly(e-caprolactone)-HEMA macromonomer.

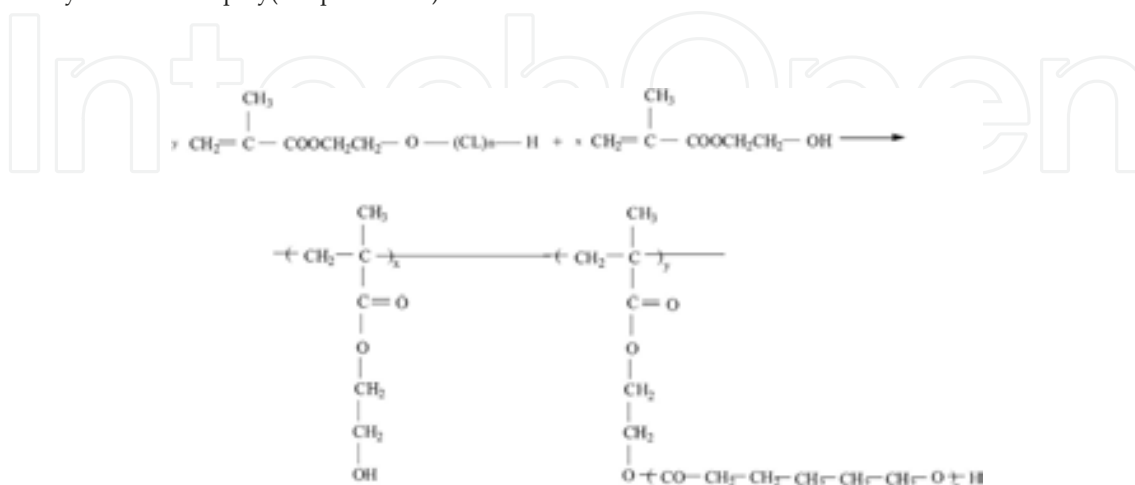


Figure 6. Synthesis of the poly(2-hydroxyethyl methacrylate)-graft-poly(e-caprolactone) copolymer.

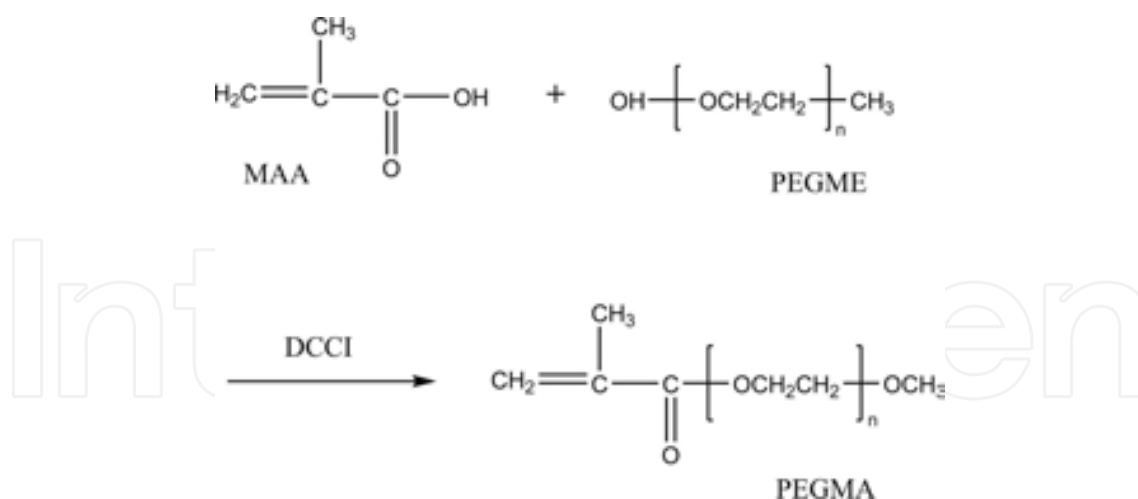


Figure 7. Dicyclohexylcarbodiimide (DCCI) method to synthesize PEG-containing macromonomers.

A semi-IPN forms when a linear polymer penetrates into another cross-linked network without any other chemical bonds between them. Semi-IPNs can more effectively preserve rapid kinetic response rates to pH or temperature due to the absence of a restricting interpenetrating elastic network while still providing the benefits like modified pore size, slow drug release, etc.

Combining of two polymers can lead to the formation of IPNs provided that one of them is already present in the solution and the other is synthesized or cross-linked in situ. This process is done by preparing a solution of monomers and initiators and then immersing a pre-polymerized hydrogel into this solution. The pore size and surface properties of an IPN can be modified to control the kinetics of drug release, environmental interactions of the hydrogel, and its mechanical features.

It is worth to point here the self-assembling peptide systems that are synthetic amino acid-based molecules which undergo a sol-gel transition when brought to neutral pH and ionic concentration. These systems do not use cross-linking agents; hence, they can safely encapsulate cells and/or drugs without exposing them to toxic agents [49] (**Figures 8 and 9**).

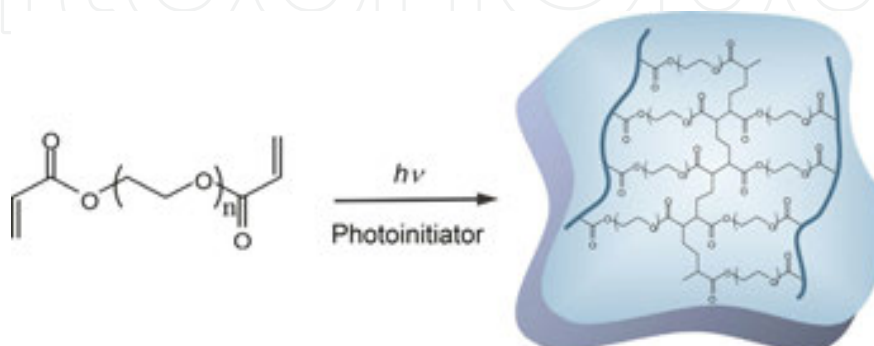


Figure 8. In situ hydrogel formation using photo-cross-linking.

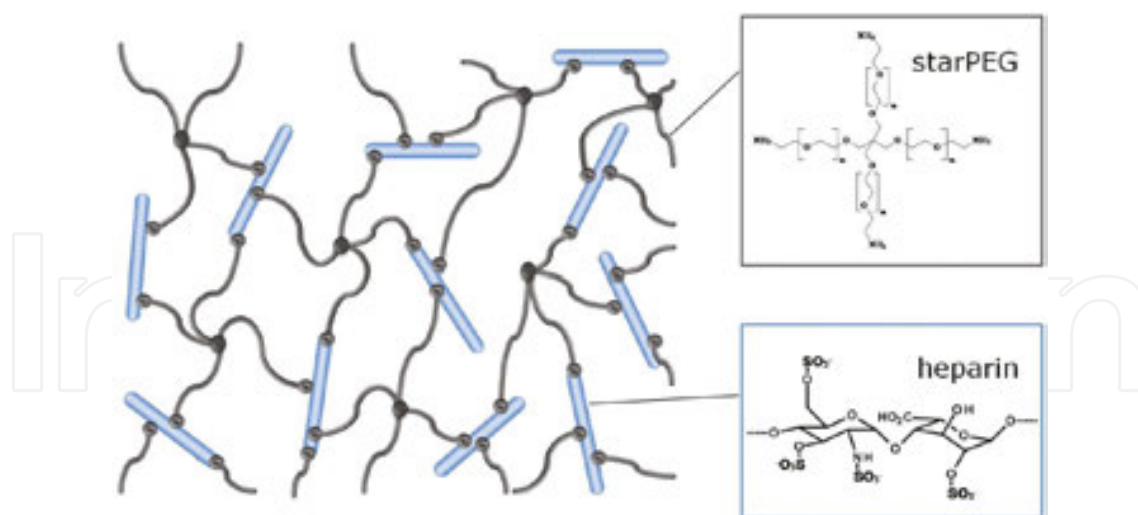


Figure 9. Hydrogel formation by cross-linking of star-PEG and heparin.

4. Some common types of hydrogels

The environment-sensitive hydrogels, also called “intelligent” or “smart” hydrogels, are currently the subject of considerable scientific research in various fields including biomedical, biotechnology, pharmaceutical, and separation science. In this section, we will introduce four classes of most used hydrogels.

4.1. pH-sensitive hydrogels

Any pH-sensitive polymer structurally contains hanging acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. ammonium salts) groups that respond to the pH changes in their environment by gain or loss of protons. Polyelectrolytes are polymers that have a large number of such ionizable groups. Anionic polyelectrolytes such as poly(acrylic acid) (PAA) are deprotonated in basic environmental conditions and then electrostatic repulsions between the chains strongly increase, which allow water molecules to penetrate causing drastic swelling of the hydrogel. However, in an acidic media, the acidic polymer protonates resulting in a decrease of charge density and polymer volume collapse (**Figure 10**). In contrast, cationic polyelectrolytes such as poly(*N,N* 9-diethylaminoethyl methacrylate) become ionized and swell in acidic pH (**Figure 10**). Amphiphilic hydrogels contain both acidic and basic moieties; therefore, they exhibit two-phase transitions in both acidic and basic environments, rather than neutral media. **Figure 11** clearly demonstrates phase transition behavior of polyelectrolyte hydrogels. Worth noting is that the phase transition from collapsed state to expanded state occurs in a small range close to the apparent dissociation constant pK_a of the hydrogel which is mostly identical with the pK_a of the ionizable groups. Approximately at the apparent pK_a of the polymer, the ionization begins and the electrostatic repulsions of the same charges present in the polymer network cause a drastic swelling of the hydrogel. If the ionization of the ionizable component

is complete, the swelling process stops and further pH increase only increases the ionic strength [7, 8]. The phase transition pH range can be modulated by selecting the ionizable moiety with a pK_a matching the desired pH range or by incorporating hydrophobic moieties into the polymer backbone [10].

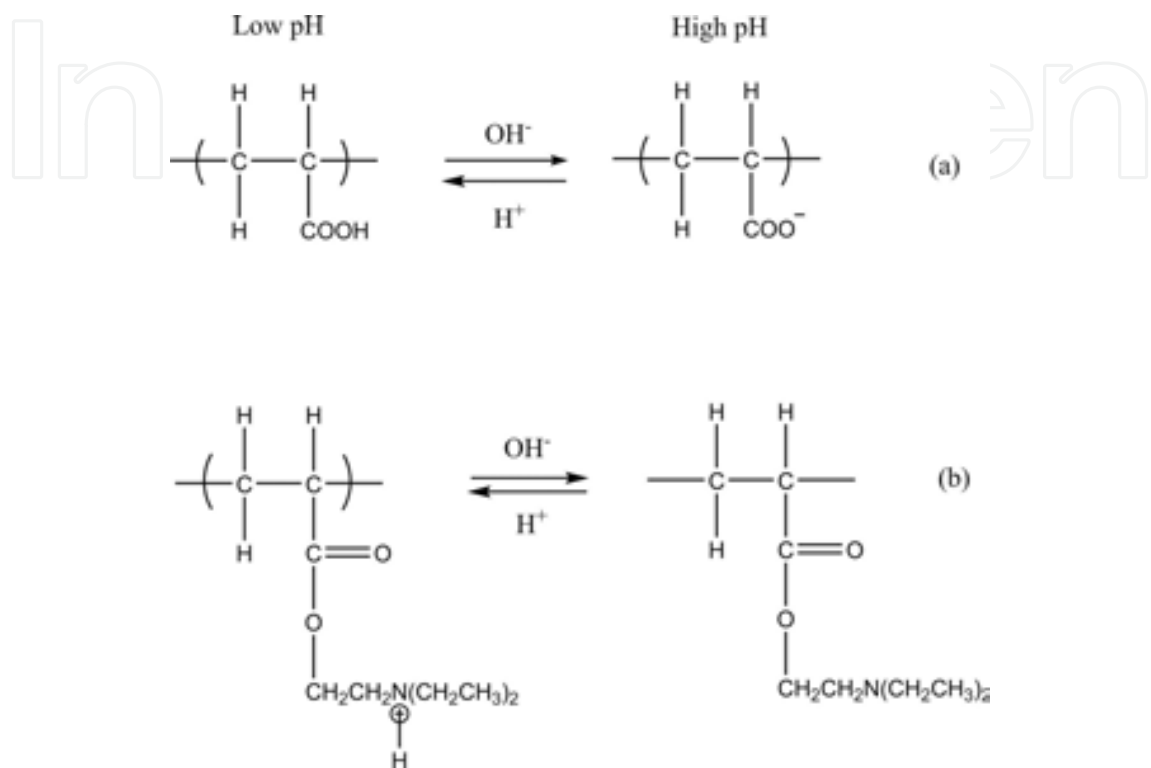


Figure 10. pH-dependent ionization of polyelectrolytes. (a) Poly(acrylic acid) and (b) poly(*N,N'*-diethylaminoethyl methacrylate).

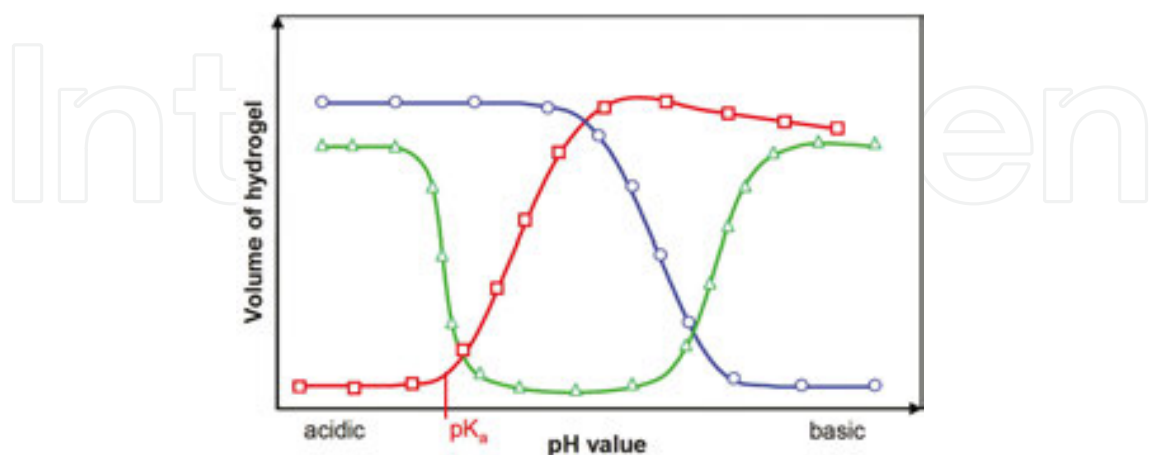


Figure 11. Phase transition behavior of polyelectrolyte hydrogels. Acidic hydrogels (\square) are ionized by deprotonation in basic solutions. Basic hydrogels (\circ) swell in acidic solutions due to the ionization of their basic groups by protonation. Amphiphilic hydrogels (Δ) contain both acidic and basic groups, therefore they show two-phase transitions.

Ionization of a polyelectrolyte takes place similar to acidic or basic groups of monoacids or monobases, but due to the electrostatic effects of neighboring groups, it will have a different dissociation constant (K_a) from corresponding monoacids or monobases.

The extent of swelling is influenced by any factor that alters this electrostatic repulsion including pH, ionic strength, and the type of counterions. **Figure 12** shows this phenomenon. In this figure, hydrogel has two phases: one phase is separated, gel-like, and formed by polymer-polymer interactions. In this condition, the maximum hydrophobicity takes place and the shrinkage of hydrogel occurs. In the second phase, interactions between the solvent and the polymer create a mixed phase in which the polymer and the aqueous solution are mixed well. The maximal value of hydrophilicity and swelling occurs in this second phase [7].

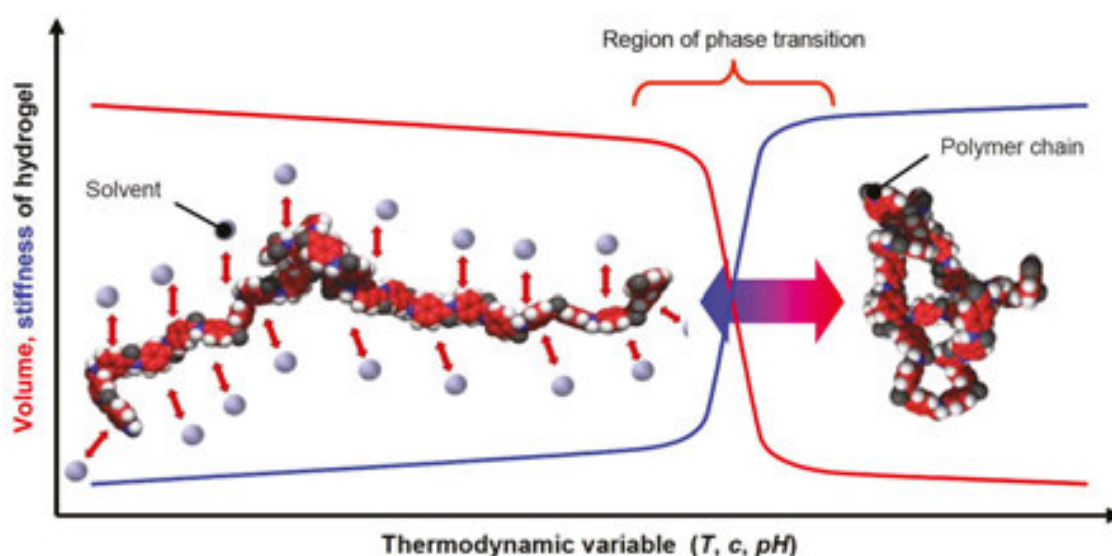


Figure 12. Phase transition behavior of stimuli-responsive hydrogels.

Different pH-sensitive behaviors and degrees of swelling can be achieved by using different monomers. The most commonly studied ionic polymers for pH-responsive behavior include poly(acrylamide) (PAAm), PAA, poly(methacrylic acid) (PMAA), poly(diethylaminoethyl methacrylate) (PDEAEMA), and poly(dimethylaminoethyl methacrylate) (PDMAEMA). Polymers containing phosphoric acid derivatives have also been reported.

4.2. Temperature-sensitive hydrogels

Temperature-sensitive hydrogels (thermogels) are aqueous monomer/polymer solutions, which have the ability to form a gel upon temperature change and have a slightly hydrophobic characteristic due to the presence of groups such as methyl, ethyl, and propyl, which preferably interact with water molecules by hydrogen bonds that cause the hydrogel to swell. These hydrogen bonds are correlated to the temperature. The structures of some of the temperature-sensitive hydrogels are shown in **Figure 13**.

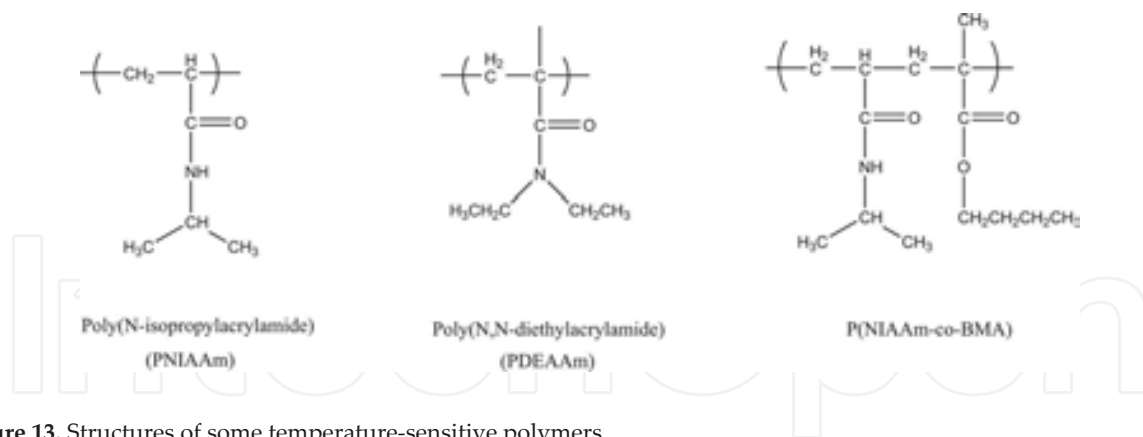


Figure 13. Structures of some temperature-sensitive polymers.

As can be seen, the common characteristic of temperature-sensitive polymers is the presence of hydrophobic groups. Most polymers increase their water solubility as the temperature increases. However, in some cases water solubility decreases with an increase in temperature (inverse or negative temperature dependence) [9]. This unusual behavior produces a phenomenon of polymer phase transition as the temperature is raised to a critical value called the “lower critical solution temperature” or LCST, which is an entropy-driven process. In the case of hydrogels with negative thermosensitivity, right below the LCST, water is a good solvent for the polymer, and hydrogen bonding interactions between the polymer and water molecules lead to enhanced dissolution in water. However, when the temperature exceeds the LCST, these interactions are broken, and the polymer chains collapse and then precipitate in the media [10, 11]. These types of hydrogels comprise polymer chains that either possess moderately hydrophobic segments (if too hydrophobic, the polymer chains will not dissolve in water at all) or contain a mixture of hydrophilic and hydrophobic groups.

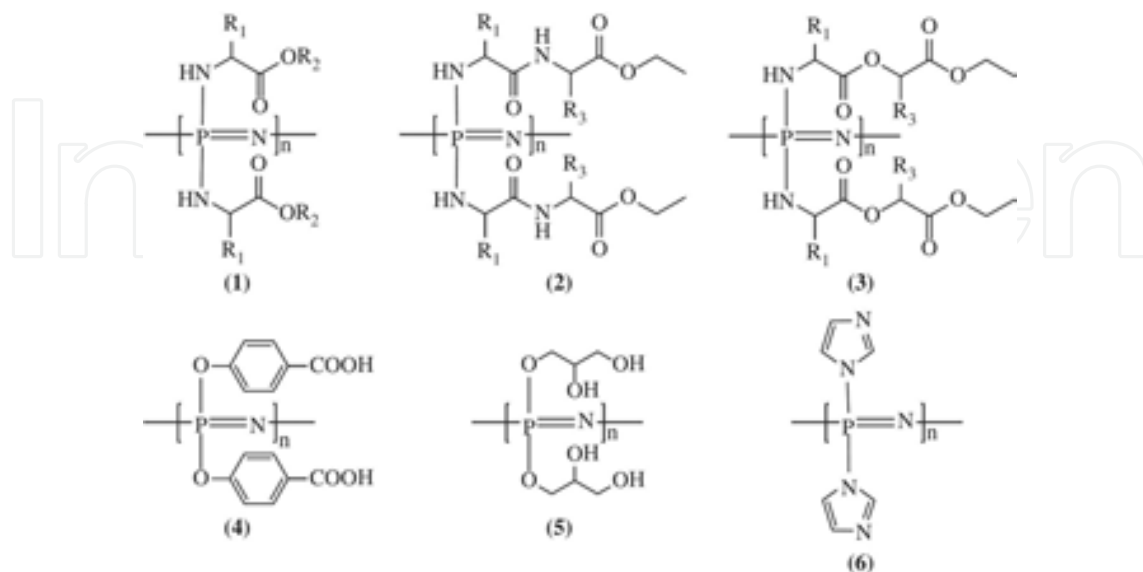


Figure 14. Some examples of poly(organophosphazene) thermogels.

As the temperature increases, positive thermosensitive hydrogels exhibit just the opposite behavior of negative thermosensitive hydrogels. The LCST of hydrogels can be modulated to increase by adding a hydrophilic component, or to decrease with a hydrophobic one. Due to this property, temperature-sensitive hydrogels swell below the LCST and collapse in an aqueous environment above this temperature, being thus suitable for controlled drug delivery. Among others, poly(*N*-isopropylacrylamide) (PNIPAM) is the most studied thermosensitive hydrogel in tissue engineering investigations. This is due to the ability of PNIPAM to squeeze out the absorbed drug when temperature is near that of the human body [19].

Other examples of thermosensitive hydrogels are collagen, agarose, hyaluronic acid, poly(organophosphazenes), and chitosan [58, 59] (**Figure 14**).

4.3. Electro-sensitive hydrogels

Electro-sensitive hydrogels, as the name indicates, undergo shrinking or swelling in the presence of an applied electric field. Like pH-sensitive hydrogels, they are usually composed of polyelectrolytes. Under the influence of an electric field, a force on counterions and immobile charged groups is produced in the network, which attracts mobile ions to the electrodes. As a result, the hydrogel can swell and shrink regionally at the cathode and anode, respectively. This phenomenon leads to bending of the hydrogel, which is caused by ion concentration difference inside the hydrogel network and culture medium and can be explained by Flory's theory of osmotic pressure [12–17]. The extent of bending depends on hydrogel structure and electrical field characteristics including strength, direction, and duration of the electrical stimulus. Electro-sensitive hydrogels can selectively be permeable for a specific molecular size and adjust the water permeability by expanding and contracting in micropore size under electrical stimulation [18]. Because electro-responsive hydrogels can transform electrical energy into mechanical energy and have promising applications in biomechanics, sensing, energy transduction, sound dampening, chemical separations, controlled drug delivery [33], and tissue engineering [20, 21], these polymers are an increasingly important class of smart materials. Hydrogels of acrylamide and carboxylic acid derivatives like PAA have been utilized as electro-sensitive and biocompatible smart muscle-based devices [22, 23].

4.4. Light-responsive hydrogels

Photo-responsive hydrogels undergo a change in their properties when irradiated with light of the appropriate wavelength. Typically, these changes are the result of light-induced structural transformations of specific functional groups along the polymer backbone or side chains. Light-sensitive hydrogels can expand and contract upon exposure to ultraviolet (UV) or visible light. Visible light offers many advantages over UV light including wide availability, low cost, ease of manipulation, and clean operation. The mechanism of visible light-induced volume change of hydrogels is based on the induction of temperature changes by incorporating a photo-responsive functional group (chromophore) (e.g. trisodium salt of copper chlorophyllin) into the polymer network. Under exposure to a specific wavelength, the chromophore absorbs light which is then dissipated locally as heat, increasing the "local" temperature of the hydrogel [26]. The resulting temperature change alters the swelling behavior of the thermo-

sensitive hydrogel [9]. Because of the thermal nature of the infrared radiation, it can also be used to elicit a hydrogel response in the absence of chromophores. If an additional functional group, such as an ionizable moiety of PAA, is incorporated into the hydrogel network, the light-responsive hydrogels become sensitive to pH changes also. This type of hydrogel can be induced to shrink by visible light and can be induced to swell by increasing the pH. The UV-sensitive hydrogels can be synthesized by introducing a leuco derivative molecule into the polymer network. Leuco derivatives are normally neutral but dissociate into ion pairs upon UV exposure. At a fixed temperature, the hydrogels discontinuously swelled in response to UV irradiation but shrank when the UV light was removed [24]. The potential applications of light-responsive hydrogels in the development of artificial muscles [25, 64], reversible valves in microfluidic devices [65], and temporal drug delivery were proposed.

5. Applications of hydrogels

Hydrogels are used in many fields. This is due to their specific structures and compatibility with different conditions of use. Flexibility of hydrogels, which is because of their water content, makes it possible to use them in different conditions ranging from industrial to biological, and the biocompatibility of the materials used to produce them and also their chemical behavior in biological environments, which can be nontoxic, extends their applications to the medical sciences.

Major applications and some examples of hydrogel usages are listed below. Note that it is not a complete listing but considers the most practical applications of hydrogels in medicine and industry.

5.1. Drug delivery

Controlled drug delivery systems (DDS), which are used to deliver drugs at certain rates for predefined periods of time, have been used to overcome the limitations of regular drug formulations. The marvelous properties of hydrogels make them a great choice in drug delivery applications. The hydrogel structures with high porosity can be obtained by controlling two factors: the degree of cross-linking in the matrix and the affinity of hydrogel to the aqueous environment in which swelling occurs. Due to the porous structures, hydrogels are highly permeable to different kinds of drugs and thus drugs can be loaded and, in proper conditions, released [27]. The possibility of releasing pharmaceuticals for long periods of time (sustained release) is the main advantage obtained from hydrogels in drug delivery investigations, which results in supplying a high concentration of an active pharmaceutical substance to a specific location over a long period of time.

Both physical (electrostatic interactions) and chemical (covalent bonding) strategies can be employed to enhance the binding between a loaded drug and the hydrogel matrix to extend the duration of drug release. Hydrogels can store and protect various drugs from hostile environments, and release them at a desired kinetics of the release. Drug release can be

activated on demand by local changes in pH, temperature, the presence of specific enzymes, or by remote physical stimuli.

5.1.1. pH-sensitive hydrogels in DDS

Since the pH change occurs at many specific or pathological body sites, it is one of the important environmental parameters for DDS. The human body exhibits variations of pH along the gastrointestinal tract and also in some specific areas such as certain tissues (and tumoral areas) and subcellular compartments. Both acidic and basic polymers are employed in pH-sensitive DDS. PAA, PMAA, poly(L-glutamic acid), and polymers containing sulfonamide are the most commonly used acidic polymers for drug delivery. Typical examples of the basic polyelectrolytes include poly(2-(dimethylamino) ethyl methacrylate) and poly(2-(diethylamino) ethyl methacrylate), poly(2-vinylpyridine), and biodegradable poly(β -amino ester).

pH-sensitive hydrogels were also used for extraction and determination purposes by different methodologies [28–31].

5.1.2. Temperature-sensitive hydrogels in DDS

Thermosensitive polymers, like pH-responsive systems, offer many possibilities in biomedicine.

Among many temperature-sensitive polymers, poly(*N*-isopropylacrylamide) (PNIPAAm) and poly(*N,N*-diethylacrylamide) (PDEAAm) find many applications. PDEAAm has a low value of LCST (a critical temperature below which the components of a solution with any composition are miscible) in the range of 25–32°C, which is near to normal body temperature.

5.2. Dyes and heavy metal ions removal

Heavy metal pollution is commonly found in wastewater of many industrial processes and has been known to cause severe threats to the public health and ecological systems. The removal of heavy metal ions from various water resources is of great scientific and practical interest.

Synthetic cross-linked polyacrylate hydrogels have been used to remove heavy metal toxicity from aqueous media [27]. However, application of these synthetic materials on large scales may not be a practical solution because they are very costly.

The pollution caused by heavy metal ions can be removed by well-known adsorption processes which, alongside flexibility in design and operation, offer the advantage of reusing the treated effluent. Also because of general reversibility of adsorption process, it is usually possible to regenerate the adsorbent to make the process most cost-effective.

The use of hydrogels as adsorbents for the removal of heavy metals, recovery of dyes, and removal of toxic components from various effluents has been studied. Adsorbents with carboxyl, sulfonic, phosphonic, and nitrogen groups on their surface favor metal ion adsorption [77].

The hydrogels were proven to be excellent dye adsorbent materials with extremely high amounts of methylene blue adsorption.

Among hydrogel-forming materials, polyelectrolytes have a special significance in heavy metal ions' removal. Many applications of polyelectrolytes in this area are due to their ability to bind oppositely charged metal ions to form complexes.

In fact, having both cationic and anionic charges on the micro- or nano-gel provides additional advantages for the removal of two distinct species simultaneously. Hydrogels are versatile and viable materials that show potential for environmental applications.

Chitosan, alginate, starch, and cellulose derivatives are biopolymer-based hydrogels, which were used to remove metal ions from aqueous media. It has been shown that the sorption mechanism and sorption capacity of heavy metal ions were influenced by the functional groups of the hydrogel. This is because of the participation of other processes like chelating and ion exchange rather than simple sorption in removal of metal ions [78, 79].

Chitosan-based hydrogels are applicable in the removal of heavy metal ions due to the presence of multiple amino (NH_2) and hydroxyl (OH) groups in their structure. This applicability originates from the tendency of metal ions to form chelates with the so-called amino groups. But after reaction of chitosan with cross-linkers, its alkalescence which is related to adsorption capacity is decreased. Chemical modification of these functional groups can improve not only the adsorption capacity but also the physicochemical properties of chitosan [79, 80]. Different approaches were employed by researchers to modify chitosan including the use of amino acid esters, oxo-2-glutaric acid, pyridyl, ethylenediamine, carbodiimide, aromatic polyimides, amine-functionalized magnetic nanoparticles, and glycine [81–83]. It is shown in these studies that both adsorption capacity and mechanical resistance of chitosan-based hydrogels will improve after modification of functional groups.

5.3. Scaffolds in tissue engineering

Tissue engineering is defined as a combination of materials, engineering, and cells to improve or replace biological organs. This needs finding proper types of cells and culturing them in a suitable scaffold under appropriate conditions. Hydrogels are an appealing scaffold material because their structures are similar to the extracellular matrix of many tissues, they can often be processed under relatively mild conditions, and they may be delivered in a minimally invasive manner [32]. Adequate scaffold design and material selection for each specific application depends on several variables, including physical properties, mass transport properties, and biological properties and is specified by the intended scaffold application and environment into which the scaffold will be placed. For example, the type of scaffold used to produce artificial skin must be different from that used for artificial bone and thus different structures for materials are needed.

Both synthetic and naturally derived materials can be used to form hydrogels for tissue engineering scaffolds.

Synthetic hydrogels are interesting because it is easy to control their chemistry and structure and thus alter their properties. Examples of polymeric synthetic materials which can be used to form hydrogels are poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA) and poly(propylene fumarate) (PPF) [33] (**Figure 15**).

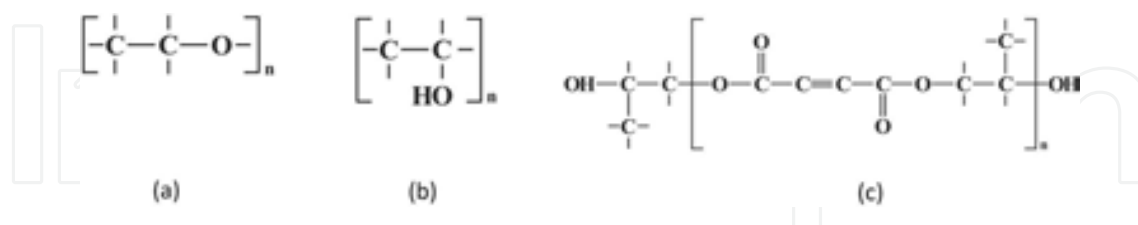


Figure 15. Structure of synthetic hydrogel-forming polymers: (a) PEO, (b) PVA (100% hydrolyzed), and (c) PPF.

Naturally derived hydrogel-forming polymers are other candidates for use in tissue engineering scaffolds because they either are natural extracellular matrix components or have properties similar to these matrices and they interact in a favorable manner in vivo. Examples are alginate and chitosan [32–34] (**Figure 16**).

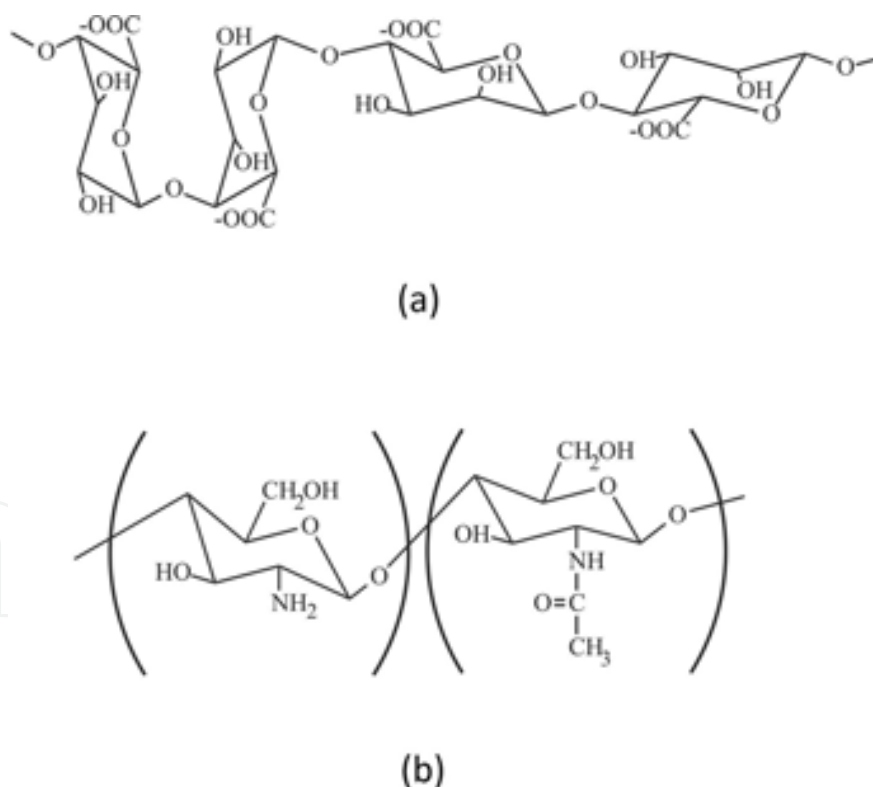


Figure 16. Structure of naturally derived hydrogel-forming polymers: (a) alginate and (b) chitosan.

Hydrogels are used for three purposes in tissue engineering applications. They may be used as agents for filling vacant spaces, carriers for delivery of bioactive molecules, and 3D structures that act as a support for cells and help the formation of an ideal tissue.

Agents for filling vacant spaces (space-filling agents) include scaffolds that provide bulking, prevent adhesions, or act as bioadhesives [33]. To reach this aim, the most basic design requirements for a hydrogel are the abilities to keep a desired volume and structural integrity for the required time.

Hydrogel scaffolds based on alginate, chitosan, and collagen show potential for use as general bulking agents. Synthetic hydrogels are often used as anti-adhesive materials because cells lack adhesion receptors to them and proteins often do not readily absorb to them if designed appropriately. Polyethylene glycol (PEG) has been used to prevent post-operative adhesions [32, 33].

Hydrogels composed of chitosan and chitin derivatives are now used as biological adhesives in surgical procedures to seal small wounds out of which air and body fluids could leak, and to improve the effectiveness of wound dressings [37, 38].

Another application of scaffold hydrogels that is quite different includes using them as vehicles to stabilize and deliver bioactive molecules to the target tissues and to encapsulate secretory cells. Currently, most drugs are delivered into patients systemically without the use of a scaffold, so large doses are usually required for a desired local effect because of enzymatic degradation of the drug and nonspecific uptake by other tissues. This is a costly process and can cause serious side effects. In addition, many factors, which are necessary or beneficial to the target tissue, may be toxic to other tissues. Thus, a vehicle or scaffold allowing for local and specific delivery to the desired tissue site is highly desirable in many situations. Ionically cross-linked alginate hydrogels and glutaraldehyde cross-linked collagen sponges are some of the examples to fulfill this requirement [39, 40].

As hydrogels are highly hydrated 3D networks of polymers, they can provide chemical and mechanical signals and also an environment for cells to adhere, proliferate, and differentiate; thus, they are suitable for cell delivery and tissue development goals. Nowadays, hydrogel scaffolds are being used to produce a wide range of tissues, including cartilage, bone, muscle, fat, liver, and neurons. Based on the type of the desired tissue, different kinds of hydrogels can be utilized. For example, alginate has been used more widely than other hydrogels to assess the *in vivo* potential of hydrogel scaffolds for cartilage engineering and also as Schwann cell matrices in the area of nerve grafting, and collagen has been used for engineering large blood vessels [33].

5.4. Contact lenses

A key area in the use of synthetic hydrogels for bioapplications is ophthalmology, especially contact lenses. A contact lens is a small optical device placed directly on the cornea to alter the corneal power. The first concept of using contact lenses was described by Leonardo da Vinci in 1508; this consisted of immersing the eye in a bowl of water. At the end of 1960, poly(2-hydroxyethyl methacrylate) (PHEMA) lenses were developed by Professor Otto Wichterle; this invention represents the most important step in contact lens development and the start of soft lenses' era [41].

Direct placing of contact lenses on the surface of cornea prevents the exchange of atmospheric oxygen and thus disturbs the natural physiological metabolism of the cornea known as hypoxic stress, so a good contact lens must have maximum oxygen permeability. Mechanical stress to the cornea produces the same problems as the hypoxic stress, such as mitosis of the epithelial cells, elevated activity in protease and glycosidase, corneal sensitivity, and changes in corneal hydration and transparency. To reduce these stresses, the proper choice of contact materials and their shape are necessary.

Hydrogels used for production of contact lenses can cover most of the requirements needed when using in different physiological conditions. For a hydrogel material that is used as a contact lens, there are some necessities to make it comfortable during usage. These necessities include amount of water content, good mechanical properties, permeability toward oxygen, wettability of surface, good optical facilities, stability toward hydrolysis and sterilization, having nontoxic nature, and having enough biological tolerance for living cells.

In order to increase the water content of hydrogel and achieve an enhanced swelling effect, different types of monomers can be used. These include dihydroxy methacrylates, methacrylic acid, acrylamides, and many other monomers.

Silicone hydrogels represent an independent group of contact lens materials. The evolution of basic hydrogels gave rise to the production of this class, and they have good swelling properties and high permeability toward oxygen, which make them suitable for use in lenses. These properties are owing to their structure in which hydrophobic silicones are connected with hydrophilic chains in such a way that makes the resulting composite suitable both mechanically and optically.

High oxygen permeability is achieved with the siloxymethacrylate monomer commonly referred to as "TRIS." The methylene groups in the structure of TRIS represent the sites for hydrophilic modification (**Figure 17**).

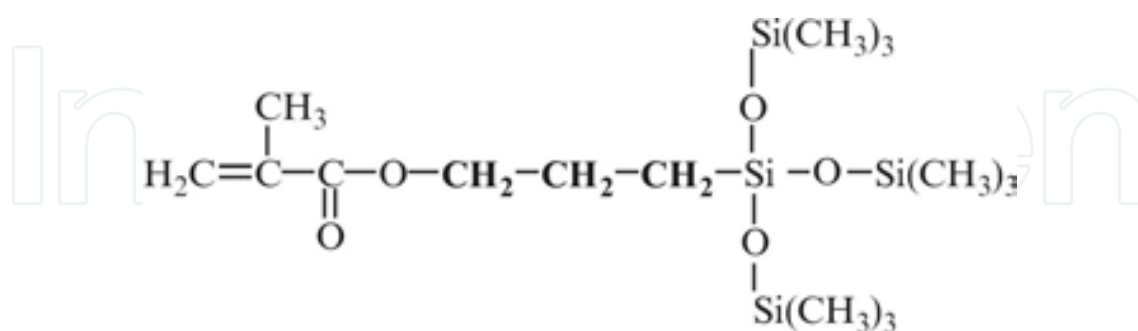


Figure 17. Structure of siloxymethacrylate monomer (TRIS).

It is possible to incorporate linear or branched hydrophilic polymer chains into the structure of the polymer to form an interpenetrated network to reduce the drying by the lenses when using them normally. This means that the "wetting chains" are fixed only by physical bonds without any covalent attachments to the patterned hydrogels' network [43].

5.5. pH-sensors

Stimuli-responsive polymers or hydrogels can change their volume significantly in response to small alterations of certain environmental parameters. Cationic polyelectrolytes dissolve (swell) more at low pH and anionic polyelectrolytes vice versa and this is due to ionization [44].

Two types of transducers are used in pH-sensitive hydrogel sensors: transducers based on mechanical work performed by hydrogel swelling and shrinking and those observing changes in properties of free swelling gels [45].

The ability of hydrogels to deform or to strain mechanically a transduction element resulting in a change of a special property of that element or in a change of a detectable distance is the basis of operation of transducers based on mechanical work of the hydrogel. They are classified as optical transducers, including reflective diaphragms and fiber Bragg grating sensors, and mechanical transducers, including microcantilevers and bending plate transducers.

Transducers of free swelling gels have to directly observe changes in one or more hydrogel properties and include optical, conductometric, and oscillating transducers. Optical transducers can directly measure changes in optical properties of hydrogels. A different approach is based on the observation of special fillings or surface coatings, which are changed or moved due to hydrogel swelling. Oscillating transducers are devices that keep changing their resonance frequency. Changes in the properties of a load result in a shift of this resonance frequency. This can be accompanied by a change of the signal amplitude. Conductometric transducers are based on measuring the conductivity of hydrogel as the degree of swelling changes [44].

5.6. Biosensors

Combining physical and chemical sensors results in a biosensor. There are two definitions for what a biosensor can do: it can be thought as a device that can sense and report a biophysical property of the system under study or a device that can deliver useful analytical information from transforming biochemical data. A common aspect in all biosensors is the presence of a biological recognition part that makes it possible to analyze biological information. Biosensors are becoming increasingly important as practical tools to cover a wide variety of application areas including point-of-care testing, home diagnostics, and environmental monitoring. Biological recognition part known as bioelement consists of different structures like enzymes, antibodies, living cells, or tissues but the point is its specificity toward one analyte and zero response to other interferents. There are various methods for coupling biomolecules with sensors including entrapment into membranes, physical adsorption, entrapment into a matrix, or covalent bonding [42, 44].

The high water content and hydrophilic nature of hydrogels are similar to the void-filling component of the extracellular matrix and render them intrinsically biocompatible. Hence, an apparent application of hydrogels in biosensors is the protection and coating function of sensor parts to prevent undesired interaction with biological molecules or cells. Hydrogels can be used as immobilization matrices for the biosensing elements and provide excellent environments for enzymes and other biomolecules to preserve their active and functional structure.

The interaction between analyte and sensing element results in a volume change in response to target component and this volume change is the basis of recognition in hydrogel-based sensors (**Figure 18**).

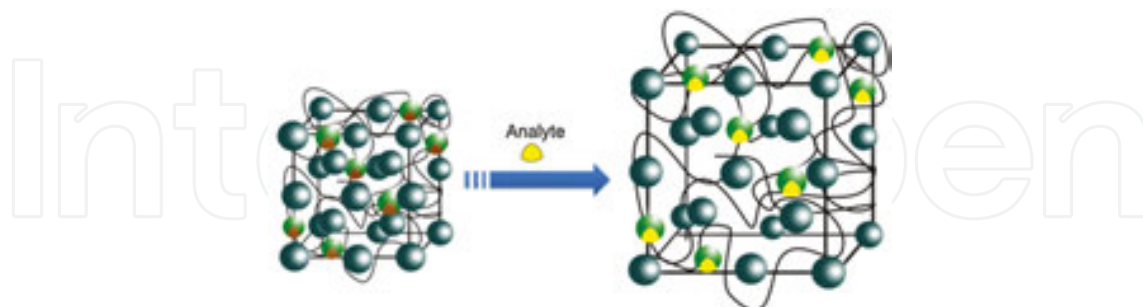


Figure 18. Volume increase of a hydrogel biosensor in response to an analyte.

Several types of sensing elements are used based on the nature of analyte but these elements can be categorized in two distinct groups: molecular interactions and living sensors.

Molecular interactions used for sensing analytes encompass different mechanisms. One of them is enzyme-substrate interactions. As enzymes are highly specific and efficient in their reactions with substrates, they may be used for precise determination of desired analytes' concentrations. There are many examples for different sensors based on enzyme-substrate interactions in hydrogel matrices including detection of organic-phase alcohols, amino acids, ammonia, urea, glucose, hydrogen peroxide, etc. Glucose-responsive hydrogels that are capable of acting as long-term insulin depots in response to increased blood glucose levels and automatically release doses of insulin at appropriate times are a promising development and could obviate the need for frequent injection and therefore provide a more convenient treatment option that would improve treatment efficacy and quality of life for hundreds of millions of people. The swelling of a hydrogel in the presence of glucose molecules makes it possible to release insulin in a controlled manner [46] (**Figure 19**).

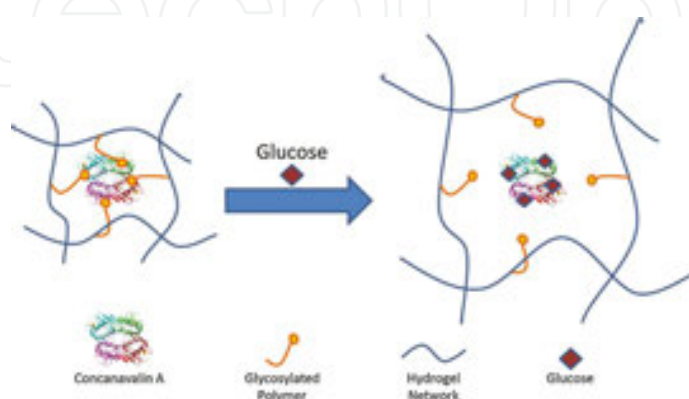


Figure 19. Concanavalin A-based glucose-responsive hydrogel swelling mechanism.

Antibody-antigen-based sensors that are affinity-based devices with a coupling of immunochemical reactions are another class of molecular interactions group. The general working principle of these sensors is based on the specific immunochemical recognition of antibodies (or antigens) immobilized on a transducer to antigen (or antibodies) that produce signals which depend on the concentration of the analyte. It is possible to use quartz crystal microgravimetry (QCM), surface plasmon resonance (SPR), or electrochemical methods for detection of the analyte.

There are several other examples of molecular interaction-based sensing of analytes like nucleotide, oligonucleotide, DNA, etc.

Another group of sensing elements is living sensors. They are combinations of hydrogels with living cells and microorganisms to form living cell-polymer composites for biosensing application. Microorganisms can detect a wide range of chemical substances, they are amenable to genetic modification and have a broad operating pH and temperature range, making them ideal as biological sensing materials. 3D structures, high water content, and biocompatibility are the main advantages of hydrogels that provide the ability to entrap cells or bacteria inside their networks enabling them to exchange gases in high rates and nourish the entrapped cells and in this way provide the possibility of usage of the cell-polymer composites in a biosensor. An instance is the use of *Arxula adeninivorans* LS3 as a biological recognition element for the rapid determination of the concentration of biodegradable pollutants in wastewater on a Clark-type oxygen electrode [47, 48].

There are two different methods to use hydrogels in biosensors: they can be coated on the surface of a sensing device like an electrode or be used as a 3D matrix or support to maintain bioelements such as cells. Preservation of cells for certain time periods in a hydrogel matrix and pathogen sensing are other examples of applications in this group (Figure 20).

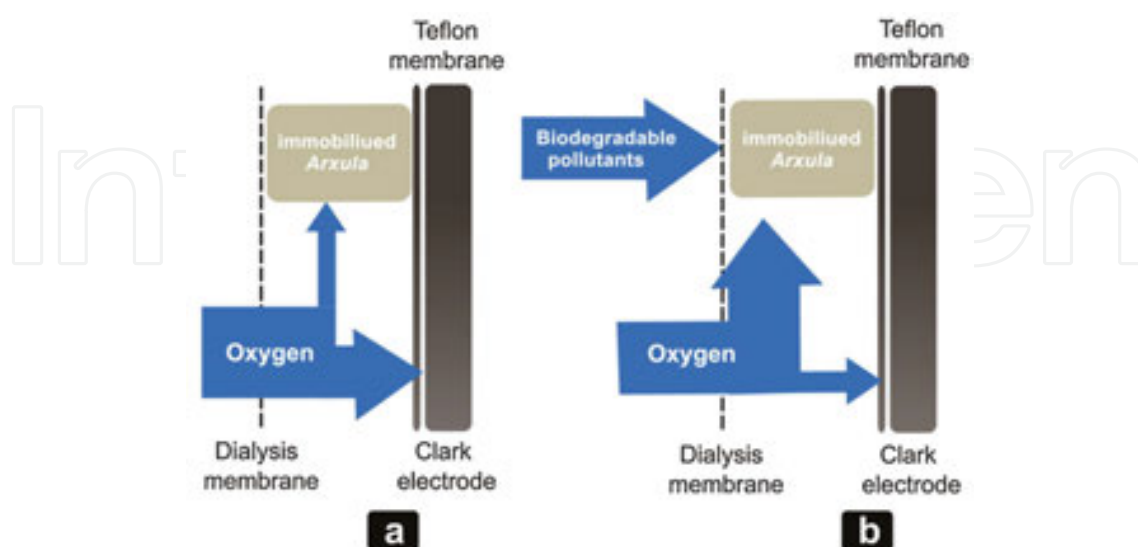


Figure 20. Schematic diagram of the *A. adeninivorans* LS3 microbial sensor illustrates the microbial consumption of dissolved oxygen (a) before and (b) after the addition of biodegradable pollutant.

5.7. Injectable hydrogel for spinal cord regeneration

Spinal cord injury (SCI) is a complex regenerative problem because of the multiple facets of growth inhibition that occur following trauma to the cord tissue. Many of these injuries do not hurt the dura mater and some of the axons are yet alive in the injury site and can be recovered. In such conditions, inserting a preformed frame or DDS into the damaged spinal cord by surgical operations may cause subsequent lesion. One alternative for this method is the use of in situ-forming scaffolds. What happens after injection into the injured cord area is the fast conversion of viscoelastic hydrogel from liquid form to gel and adaptation to the tissue of injury site [49].

The small spaces between spinal cord tissue and even transected parts formed after SCI will be filled by in vivo conversion of liquid hydrogel to the gel form. The gel, which now serves as a scaffold, will eliminate vacant spaces and forms a template for regeneration of the injured cord tissue by helping cellular penetration and matrix. In this way, it is not necessary to create preformed scaffolds for each patient individually and disconnecting viable tissue at the injury site to implant the preformed scaffold, which can cause further damage and loss of functionality, will be avoided [50, 51] (**Figure 21**).

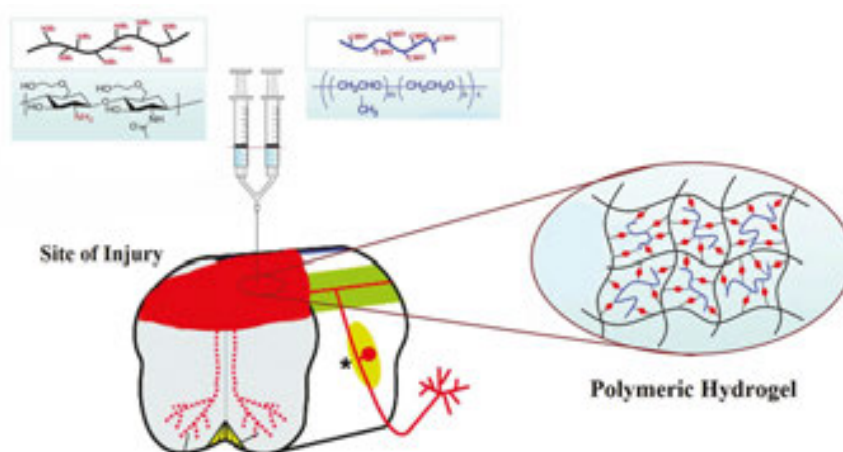


Figure 21. Injection of liquid hydrogel into the site of injury.

Injectable materials, in their liquid state, can be uniformly mixed with cells and other therapeutics prior to delivery into the injury site. The mechanical properties of gel scaffolds can more closely match the properties of the spinal cord tissue, compared to most preformed biomaterial matrices [49, 51].

There are some requirements for the design and use of injectable systems based on their functions and design parameters.

Their functions include [49, 52–54]:

1. Create a scaffold for cellular infiltration and axonal ingrowth. The gel material itself will serve to bridge the lesion site.

2. Encapsulation of drugs and maintenance of bioactivity throughout gelation and release. Injectable systems can provide a sustained and tunable delivery of these agents locally to the lesion site.
3. Support of suspended cell populations prior to injection, throughout the solidification process, and within the lesion site. Cellular therapies are more effective when delivered and maintained locally in the injured area as opposed to being delivered systemically (Figure 22).

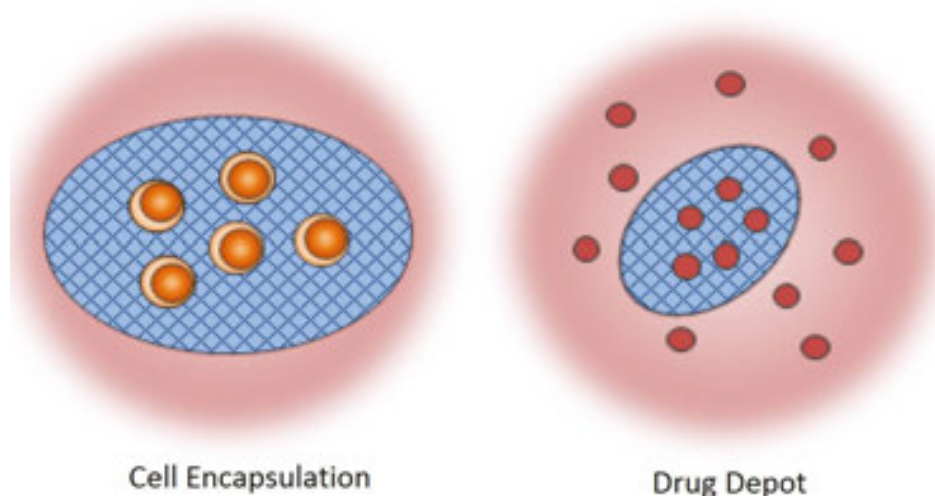


Figure 22. Functions of injectable hydrogels.

The importance of design parameters is originating from the difficulty in isolating the effects of cross-linking and macromer concentration-dependent material properties such as mechanical stiffness, mesh or pore size, degradation rate, and bioactive ligand density.

Design parameters include biocompatibility of used materials with the tissue of injured site, mild solidification conditions, suitable porosity and mesh size of the designed scaffold, mechanical properties of the gel material, degradation rate, and bioactivity [55–57].

Injectable hydrogels can be natural or synthetic with their own benefits and disadvantages. They can also be classified as physical and chemical gels [49, 62].

Generally, physical hydrogels have the limitation of weak mechanical properties; thus, a combination of chemical and physical cross-linking has been used to overcome this weakness. For example, PNIPAAm-co-glycidyl methacrylate (GMA) and polyamidoamine (PAMAM) macromers undergo a dual-hardening physical and chemical gelation process and form PNIPAAm-co-glycidyl methacrylate (GMA)/polyamidoamine (PAMAM) injectable hydrogel [58].

Injectable hydrogel systems are minimally invasive and patient friendly. Cells or bioactive molecules are easy to mix with polymer solutions and these mixtures are in situ and easily form the 3D microenvironments into any desired defect shapes.

5.8. Supercapacitor hydrogels

The fast developments in portable electronic equipments industry such as wearable devices, arbitrarily curved displays and even transparent mobile phones, require the fabrication of flexible, transparent, lightweight and efficient storage options [73]. To this end, the key issue is the simultaneous incorporation of mechanical robustness, optical transmittance, and electronic conductivity [74]. Because of the importance of high-performance flexible supercapacitors, the technique of the supercapacitors is still making rapid progresses. Recently, several strategies for flexible supercapacitors have been demonstrated, including coating active materials, such as RuO₂ [66], MnO₂ [67], V₂O₅ [68], NiOH [69], and graphene nanosheets [70] onto conductive fibers by electrochemical deposition or casting and fabrication of hydrogel or aerogel films based on graphene [73]. However, these methods suffer from several disadvantages that hinder their large-scale commercialization, such as high cost of noble metals or expensive carbon support materials, limited ionic/electronic conductivity, poor mechanical flexibility, and scalable electrochemical synthesis conditions.

Electrically conducting polymer hydrogels show great potential for the expected integration due to their excellent solid-liquid interface, good electric characteristics, and mechanical flexibility, and represent a promising material platform for emerging flexible energy storage devices [71, 72]. Conducting polymers such as polyaniline, polypyrrole, and their derivatives provide the unique electrical properties of metals or semiconductors, as well as attractive properties associated with conventional polymers, such as ease of synthesis and flexibility in processing; therefore, supercapacitor hydrogels are attracting much attention as new power sources [73]. Flexible solid-state supercapacitors provide high power density, long cycle life, and the potential to achieve relatively high energy density.

Shi et al. have recently synthesized a 3D nanostructured conductive polypyrrole hydrogel via an interfacial polymerization method [73]. The high-performance flexible solid-state supercapacitor demonstrated promising capacitive properties and good electrochemical stability during long-term cycling. So far, many aspects such as conductivity and morphology of conductive polymer hydrogels have been extensively studied. However, the combination of stretchability and transparency is unique, and particularly long cycle stability has not been achieved before. In this regard, Hao et al. demonstrated a facile and smart strategy for the preparation of structurally stretchable, electrically conductive, and optically semitransparent α -cyclodextrin polyacrylamide-polyaniline hybrid hydrogel networks as electrodes, which show a high performance in supercapacitor application [74].

6. Conclusions

This chapter aims to introduce briefly the hydrogels: a class of natural or synthetic polymeric materials that have the ability to hold huge amounts of water because of their specific structures and subsequent swelling properties. Based on this ability, they found a wide variety of applications, and because of the possibility to modify the polymeric structure to obtain

desired functionality, the areas of applications are rapidly expanding. They can be designed in such a way that they can respond to a specific stimulus including pH, temperature, light, etc. at a predefined level and thus be stimuli responsive. Among their amazing characteristics, the biocompatibility and biodegradability make them a powerful candidate to use in biological and environmental applications as implants or materials for removal of toxic pollutants. In addition, conducting hydrogels are often a good choice in designing and fabrication of supercapacitors, which promise the most rapid developments in electronics.

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